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SEAP.GLP-1GLy8
 10 20 30 40 50
 GAATTCGCGCCACCATGCTGCTGCTGCTGCTGCTGGGCCTGCGCCTG
 CTTAAGGCGGGTGGTACGACGACGACGACGACGACGACCCGGACGCGGAC
 M L L L L L L L G L R L>
 SEAP SIGNAL PEPTIDE____>
 60 70 80 90 100
 CAGCTGAGCCTGGGCCACGGCGAGGGCACCTTCACCAGCGACGTGAGCAG
 GTCGACTCGGACCCGGTGCCGCTCCCGTGGAAGTGGTCGCTGCACTCGTC
 Q L S L G>
 SEAP SIG____>H G E G T F T S D V S S
 GLP-1GLY8____>
 110 120 130 140 150
 CTACCTGGAGGGCCAGGCCGCAAGGAGTTCATCGCCTGGCTGGTGAAGG
 GATGGACCTCCCGGTCCGGCGGTTCTCAAGTAGCGGACCGACCACTTCC
 Y L E G Q A A K E F I A W L V K>
 GLP-1GLY8____>
 GCCGCGGC
 CGGCGCCG
 G R G>
 ____>

Figure 1

Exendin-4.GLP-1Gly8

```

      10      20      30      40      50
GAATTCCGCCCACCATGAAGATCATCCTGTGGCTGTGTGTGTTCCGGCCTG
CTTAAGGCGGGTGGTACTTCTAGTAGGACACCGACACACACAAGCCGGAC
      M K I I L W L C V F G L>
      PROEXENDIN>

      60      70      80      90      100
TTCCTGGCCACCCTGTTCCCCATCAGCTGGCAGATGCCCGTGGAGTCCGG
AAGGACCGGTGGGACAAGGGGTAGTCGACCGTCTACGGGCACCTCAGGCC
      F L A T L F P I S W Q M P V E S G>
      PROEXENDIN>

      110     120     130     140     150
CCTGTCCTCCGAGGACTCCGCCAGCTCCGAGAGCTTCGCCAAGCGCATCA
GGACAGGAGGCTCCTGAGGCGGTTCGAGGCTCTCGAAGCGGTTTCGCGTAGT
      L S S E D S A S S E S F A K R I>
      PROEXENDIN>

      160     170     180     190     200
AGCGCCACGGCGAGGGCACCTTCACCAGCGACGTGAGCAGCTACCTGGAG
TCGCGGTGCCGCTCCCGTGGAAGTGGTCGCTGCACTCGTCGATGGACCTC
      H G E G T F T S D V S S Y L E>
      GLP-1 GLY-8>
K R>
>

      210     220     230     240     250
GGCCAGGCCGCCAAGGAGTTCATCGCCTGGCTGGTGAAGGGCCGCGGCTG
CCGGTCCGGCGGTTCTCAAGTAGCGGACCGACCACTTCCCGGCGCCGAC
      G Q A A K E F I A W L V K G R G>
      GLP-1 GLY-8>
  
```

Figure 2

Helodermin.GLP-1Gly8

```

      10      20      30      40      50
GAATTCGCCCCACCATGAAGAGCATCCTGTGGCTGTGTGTGTTTGGCCTG
CTTAAGGCGGGTGGTACTTCTCGTAGGACACCGACACACAAACCGGAC
      M K S I L W L C V F G L>
      PRO-HELODERMIN>

      60      70      80      90      100
      *
CTGATTGCCACCCTGTTCCCTGTGAGCTGGCAGATGGCCATCAAGAGCAG
GACTAACGGTGGGACAAGGGACACTCGACCCTCTACCGGTAGTTCTCGTC
      L I A T L F P V S W Q M A I K S R>
      PRO-HELODERMIN>

      110     120     130     140     150
ACTGTCCTCTGAGGACTCTGAGACAGACCAGAGACTGAAGCGCATCAAGC
TGACAGGAGACTCCTGAGACTCTGTCTGGTCTCTGACTTCGCGTAGTTCC
      L S S E D S E T D Q R L K R I K>
      PRO-HELODERMIN>

      160     170     180     190     200
      *
GCCACGGCGAGGGCACCTTCACCAGCGACGTGAGCAGCTACCTGGAGGGC
CGGTGCCGCTCCCGTGGAAGTGGTCGCTGCACTCGTCGATGGACCTCCCG
R>
      H G E G T F T S D V S S Y L E G>
      PRODUCT=GLP-1>

      210     220     230     240
CAGGCCGCCAAGGAGTTCATCGCCTGGCTGGTGAAGGGCCGCGGC
GTCCGGCGGTTTCCTCAAGTAGCGGACCGACCACTTCCCGGCGCCG

```

```

      Q A A K E F I A W L V K G R G>
      PRODUCT=GLP-1>

```

Figure 3

GIP.GLP-1Gly8

```

      10      20      30      40      50
GAATTCGCCCCACCATGGTGGCCACCAAGACCTTTGCCCTGCTGCTCCTG
CTTAAGGCGGGTGGTACCACCGGTGGTTCTGGAAACGGGACGACGAGGAC
      M V A T K T F A L L L L>
      PRO-GIP>

      60      70      80      90      100
      *
AGCCTCTTCCTGGCTGTGGGACTGGGCGAGAAGAAGGAAGGCCACTTCAG
TCGGAGAAGGACCGACACCCTGACCCGCTCTTCTTCCTTCCGGTGAAGTC
S L F L A V G L G E K K E G H F S>
      PRO-GIP>

      110     120     130     140     150
CGCCCTGCCCAGCCTGCCAGTGGGCAGCCATGCCAAGGTGAGCTCCCCAC
GCGGGACGGGTTCGGACGGTCACCCGTCGGTACGGTTCCACTCGAGGGGTG
A L P S L P V G S H A K V S S P>
      PRO-GIP>

      160     170     180     190     200
      *
AGAAGCGCATCAAGCGCCACGGCGAGGGCACCTTCACCAGCGACGTGAGC
TCTTCGCGTAGTTTCGCGGTGCCGCTCCCGTGGAAGTGGTCGCTGCACTCG
Q K R I K R>
      PRO-GIP>H G E G T F T S D V S>
      GLP-1GLY8>

      210     220     230     240     250
AGCTACCTGGAGGGCCAGGCCGCCAAGGAGTTCATCGCCTGGCTGGTGAA
TCGATGGACCTCCCGGTCCGGCGGTTCTCAAGTAGCGGACCGACCACTT
S Y L E G Q A A K E F I A W L V K>
      GLP-1GLY8>

      260
GGGCCGCGGC
CCCGGCGCCG
G R G>
      >
  
```

Figure 4

IGF-1(furin).GLP-1Gly8

```

      10      20      30      40      50
GAATTCCGCCCACCATGGGCAAGATCAGCAGCCTGCCCACCCAGCTGTTC
CTTAAGGCGGGTGGTACCCGTTCTAGTCGTCGGACGGGTGGGTCGACAAG

      M  G  K  I  S  S  L  P  T  Q  L  F >
      _____IGF1 1-48_____>

      60      70      80      90      100
      *
AAGTGCTGCTTTTGTGACTTCCTGAAGGTGAAGATGCACACCATGAGCTC
TTCACGACGAAAACACTGAAGGACTTCCACTTCTACGTGTGGTACTCGAG
  K  C  C  F  C  D  F  L  K  V  K  M  H  T  M  S  S>
      _____IGF1 1-48_____>

      110     120     130     140     150
CAGCCACCTGTTCTACCTGGCCCTGTGCCTGCTGACCTTCACCAGCTCCG
GTCGGTGGACAAGATGGACCGGGACACGGACGACTGGAAGTGGTTCGAGGC
  S  H  L  F  Y  L  A  L  C  L  L  T  F  T  S  S>
      _____IGF1 1-48_____>

      160     170     180     190     200
      *
CCACAGCCAAGCGCATCAAGCGCCACGGCGAGGGCACCTTCACCAGCGAC
GGTGTTCGGTTCGCGTAGTTTCGCGGTGCCGCTCCCGTGGAAGTGGTCGCTG
A  T  A>
      _____>K  R  I  K  R>
      _____FURIN CL_____>H  G  E  G  T  F  T  S  D>
      _____PRODUCT=GLP-1_____>

      210     220     230     240     250
GTGAGCAGCTACCTGGAGGGCCAGGCCGCCAAGGAGTTCATCGCCTGGCT
CACTCGTTCGATGGACCTCCCGGTCCGGCGGTTTCCTCAAGTAGCGGACCGA
  V  S  S  Y  L  E  G  Q  A  A  K  E  F  I  A  W  L>
      _____PRODUCT=GLP-1_____>

      260
GGTGAAGGGCCGCGGC
CCACTTCCCGGCGCCG
  V  K  G  R  G>
      _____PRODUCT=_____>
  
```

Figure 5

IGF-I.GLP-1GLy8

10 20 30 40 50
 GAATTCCGCCCCACCATGGGCAAGATCAGCAGCCTGCCCCACCCAGCTGTTC
 CTTAAGGCGGGTGGTACCCGTTCTAGTCGTCGGACGGGTGGGTGCGACAAG
 M G K I S S L P T Q L F>
 IGF-I SIGNAL PEPTIDE>

60 70 80 90 100
 AAGTGCTGCTTTTGTGACTTCCTGAAGGTGAAGATGCACACCATGAGCTC
 *

TTCACGACGAAAACACTGAAGGACTTCCACTTCTACGTGTGGTACTCGAG
 K C C F C D F L K V K M H T M S S>
 IGF-I SIGNAL PEPTIDE>

110 120 130 140 150
 CAGCCACCTGTTCTACCTGGCCCTGTGCCTGCTGACCTTCACCAGCTCCG
 GTCGGTGGACAAGATGGACCGGGACACGGACGACTGGAAGTGGTCGAGGC
 S H L F Y L A L C L L T F T S S>
 IGF-I SIGNAL PEPTIDE>

160 170 180 190 200
 CCACAGCCCCACGGCGAGGGCACCTTCACCAGCGACGTGAGCAGCTACCTG
 GGTGTCGGGTGCCGCTCCCGTGGAAGTGGTCGCTGCACTCGTCGATGGAC
 A T A>
 >H G E G T F T S D V S S Y L>
 GLP-1GLY8>

210 220 230 240 250
 GAGGGCCAGGCCGCCAAGGAGTTCATCGCCTGGCTGGTGAAGGGCCGCGGC
 CTCCCGGTCCGGCGGTTCTCAAGTAGCGGACCGACCACTTCCCGGCGCCG
 E G Q A A K E F I A W L V K G R G>
 GLP-1GLY8>

Figure 6

Preproglucagon.GLP-1Gly8

```

      10      20      30      40      50
GAATTCCGCCCACCATGAAAAGCATTTACTTTGTGGCTGGGCTGTTTGTG
CTTAAGGCGGGTGGTACTTTTCGTAAATGAAACACCGACCCGACAAACAC
      M K S I Y F V A G L F V>
      _____GLUCAGON SIGNAL PEPTIDE_____>

      60      70      80      90      100
ATGCTGGTGCAAGGCAGCTGGCAACACGGCGAGGGCACCTTCACCAGCGA
TACGACCACGTTCCGTCGACCGTTTGTGCCGCTCCCGTGGAAGTGGTCGCT
      M L V Q G S W Q>
      _____GLUCAGON SIGNAL P_____>H G E G T F T S D>
      _____GLP-1GLY8_____>

      110      120      130      140      150
CGTGAGCAGCTACCTGGAGGGCCAGGCCGCCAAGGAGTTCATCGCCTGGC
GCACTCGTCGATGGACCTCCCGGTCCGGCGGTTCTCAAGTAGCGGACCG
      V S S Y L E G Q A A K E F I A W>
      _____GLP-1GLY8_____>

      160
TGGTGAAGGGCCGCGGC

```

```

ACCACTTCCCGGCGCCG
L V K G R G>
_____GLP-1GLY8_____>

```

Figure 7

Alpha-1 antitrypsin.GLP-1Gly8

```

      10      20      30      40      50
GAATTCCGCCCACCATGCCCTCTTCTGTCTCCTGGGGCATCCTCCTGCTG
CTTAAGGCGGGTGGTACGGGAGAAGACAGAGGACCCCGTAGGAGGACGAC
      M P S S V S W G I L L L>
      _____A1AT SIGNAL PEPTIDE_____>

      60      70      80      90      100
GCAGGCCTGTGCTGCCTGGTCCCTGTCTCCCTGGCTCACGGCGAGGGCAC
CGTCCGGACACGACGGACCAGGGACAGAGGGACCGAGTGCCGCTCCCGTG
A G L C C L V P V S L A>
      _____A1AT SIGNAL PEPTIDE_____>H G E G T>
      _____>

      110      120      130      140      150
CTTCACCAGCGACGTGAGCAGCTACCTGGAGGGCCAGGCCGCAAGGAGT
GAAGTGGTCGCTGCACTCGTCGATGGACCTCCCGGTCCGGCGGTTTCCTCA
F T S D V S S Y L E G Q A A K E>
      _____GLP-1GLY8_____>

      160      170
TCATCGCCTGGCTGGTGAAGGGCCGCGGC
AGTAGCGGACCGACCACTTCCCGGCGCCG
F I A W L V K G R G>
      _____GLP-1GLY8_____>
  
```

Figure 8

Factor IX.GLP-1Gly8

```

      10      20      30      40      50
GAATTCCGCCCACCATGCAGAGAGTGAACATGATCATGGCAGAAATCCCCA
CTTAAGGCGGGTGGTACGTCTCTCACTTGTACTAGTACCGTCTTAGGGGT
      M Q R V N M I M A E S P>
      PRO-FIX
      60      70      80      90      100
      *
GGCCTGATCACCATCTGCCTCCTGGGATACCTCCTGTCTGCTGAGTGAC
CCGGACTAGTGGTAGACGGAGGACCTATGGAGGACAGACGACTCACGTG
  G L I T I C L L G Y L L S A E C T>
      PRO-FIX
      110     120     130     140     150
AGTGTTCCTGGACCATGAGAATGCCAACAAGATTCTGAACAGACCCAAGA

TCACAAGGACCTGGTACTCTTACGGTTGTTCTAAGACTTGTCTGGGTTCT
  V F L D H E N A N K I L N R P K>
      PRO-FIX
      160     170     180     190     200
      *
GGCATGGGGAGGGGCACCTTCACCAGCGACGTGAGCAGCTACCTGGAGGGC
CCGTACCCCTCCCGTGGAAAGTGGTCGCTGCACTCGTCGATGGACCTCCCG
R>
__>H G E G T F T S D V S S Y L E G>
      GLP-1GLY-8
      210     220     230     240
CAGGCCGCCAAGGAGTTCATCGCCTGGCTGGTGAAGGGCCGCGGC
GTCCGGCGGTTTCCTCAAGTAGCGGACCGACCACTTCCCGGCGCCG
  Q A A K E F I A W L V K G R G>
      GLP-1GLY-8
  
```

Figure 9

Exendin-4 (IGF-I) .GLP-1GLY8

10 20 30 40 50
 GAATTCGCGCCACCATGAAGATCATCCTGTGGCTGTGTGTGTTTCGGCCTG
 CTTAAGGCGGGTGGTACTTCTAGTAGGACACCGACACACACAAGCCGGAC
 M K I I L W L C V F G L>
 PRO-EXENDIN-4>

60 70 80 90 100
 *
 TTCCTGGCCACCCTGTTCCCATCAGCTGGCAGATGCCCGTGGAGTCCGG
 AAGGACCGGTGGGACAAGGGGTAGTCGACCGTCTACGGGCACCTCAGGCC
 F L A T L F P I S W Q M P V E S G>
 PRO-EXENDIN-4>

110 120 130 140 150
 CCTGTCCTCCGAGGACTCCGCCAGCTCCGAGAGCCCTCTGAAGCCTGCCA
 GGACAGGAGGCTCCTGAGGCGGTGAGGCTCTCGGGAGACTTCGGACGGT
 L S S E D S A S S E S>
 PRO-EXENDIN-4>P L K P A>
 IGF-I PRO>

160 170 180 190 200
 *
 AGTCTGCCAGACATGGAGAGGGCACCTTCACATCTGACGTGAGCAGCTAC
 TCAGACGGTCTGTACCTCTCCCGTGGGAAGTGTAGACTGCACTCGTCGATG
 H G E G T F T S D V S S Y>
 GLP-1GLY8>
 K S A R>

210 220 230 240 250
 CTGGAGGGGCCAGGCCGCCAAGGAGTTCATCGCCTGGCTGGTGAAGGGCCGCGGC
 GACCTCCCGGTCCGGCGGTTCTCAAGTAGCGGACCGACCACTTCCCGGCGCCG
 L E G Q A A K E F I A W L V K G R G>
 GLP-1GLY8>

Figure 10

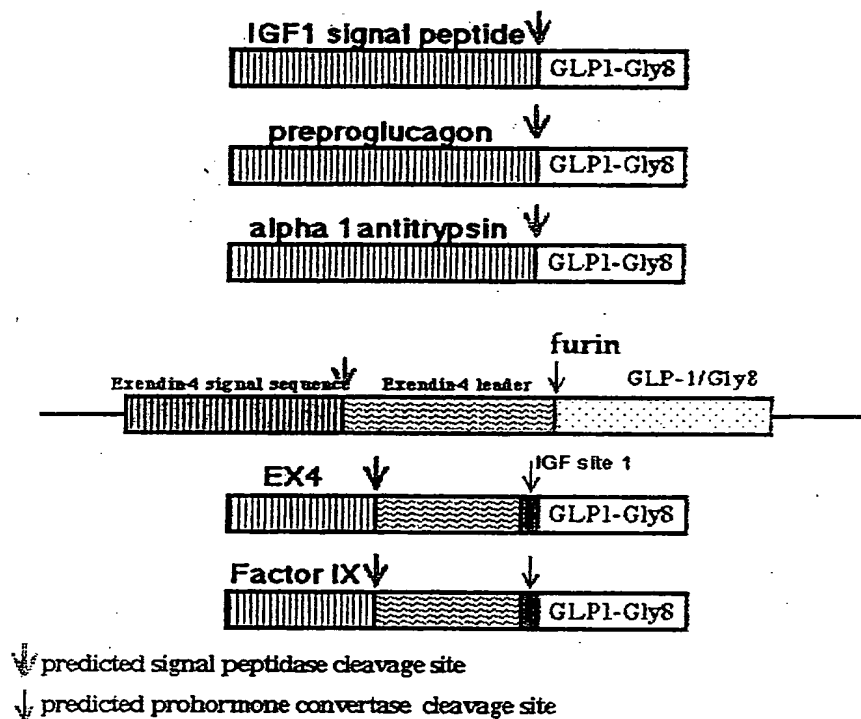


Figure 11

GLP-1 Expression Levels in the Supernatant of Transfected 293 Cells

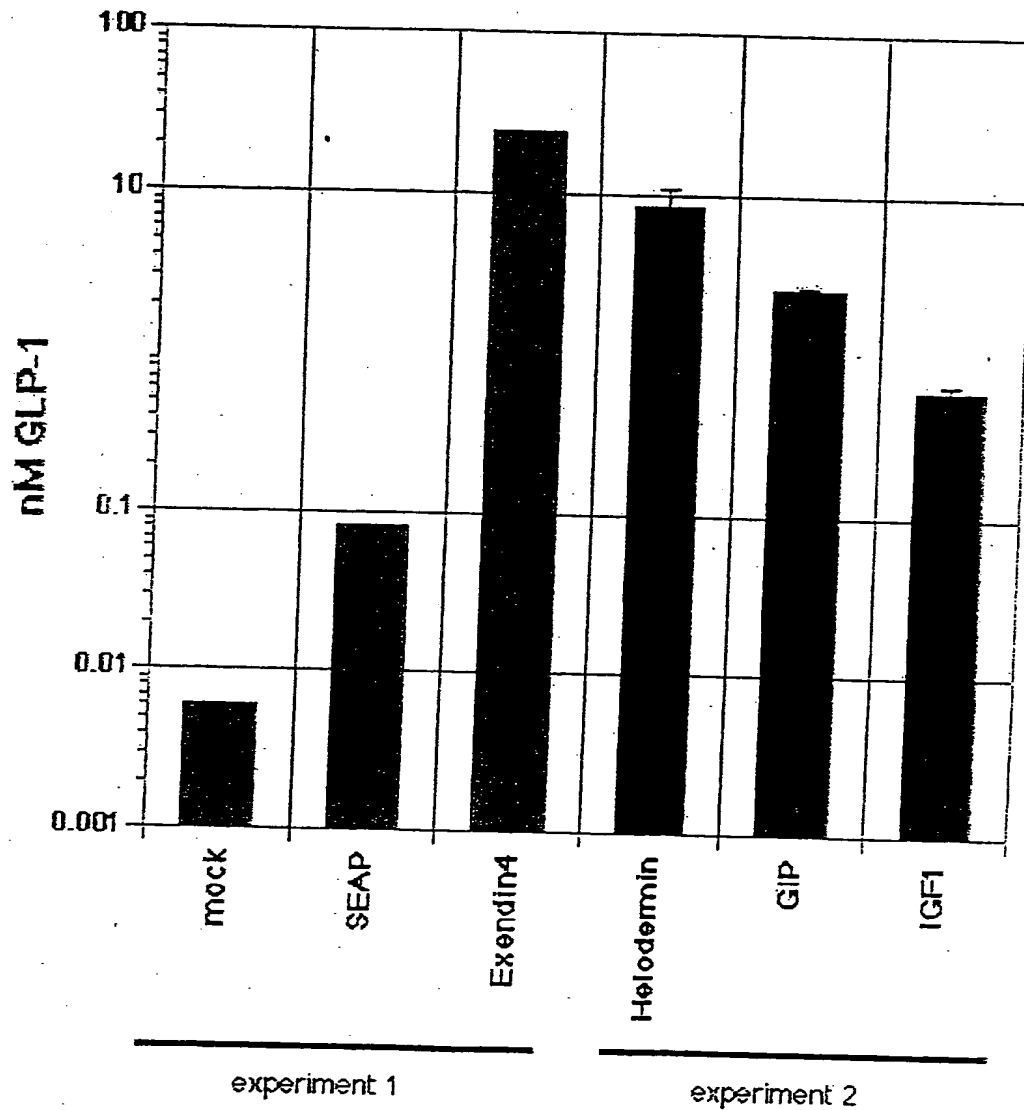


Figure 12

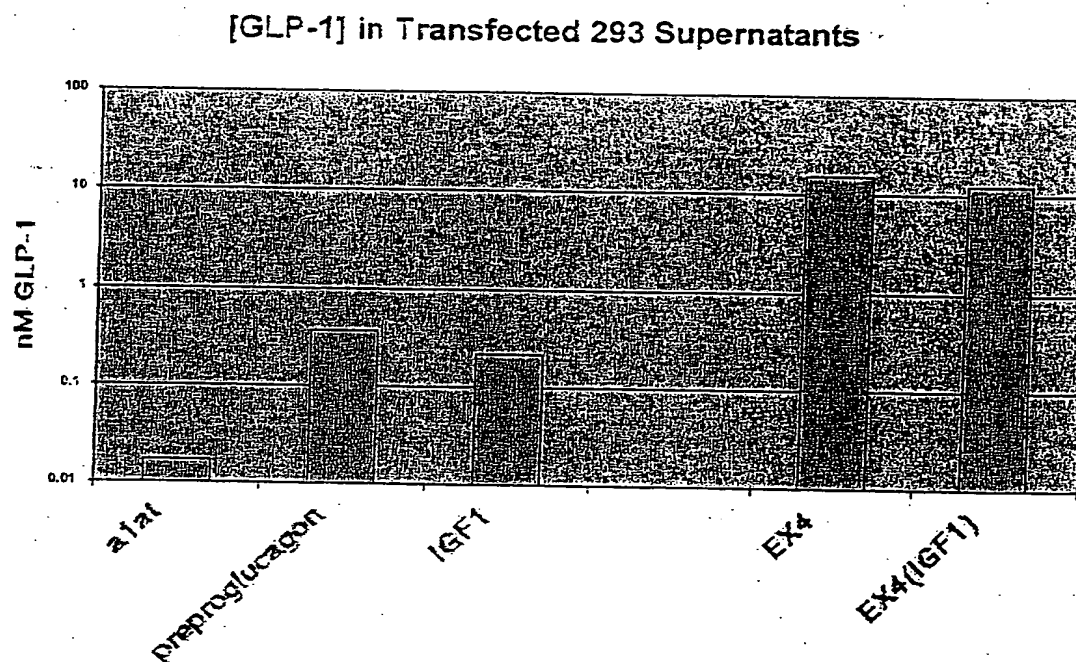


Figure 13

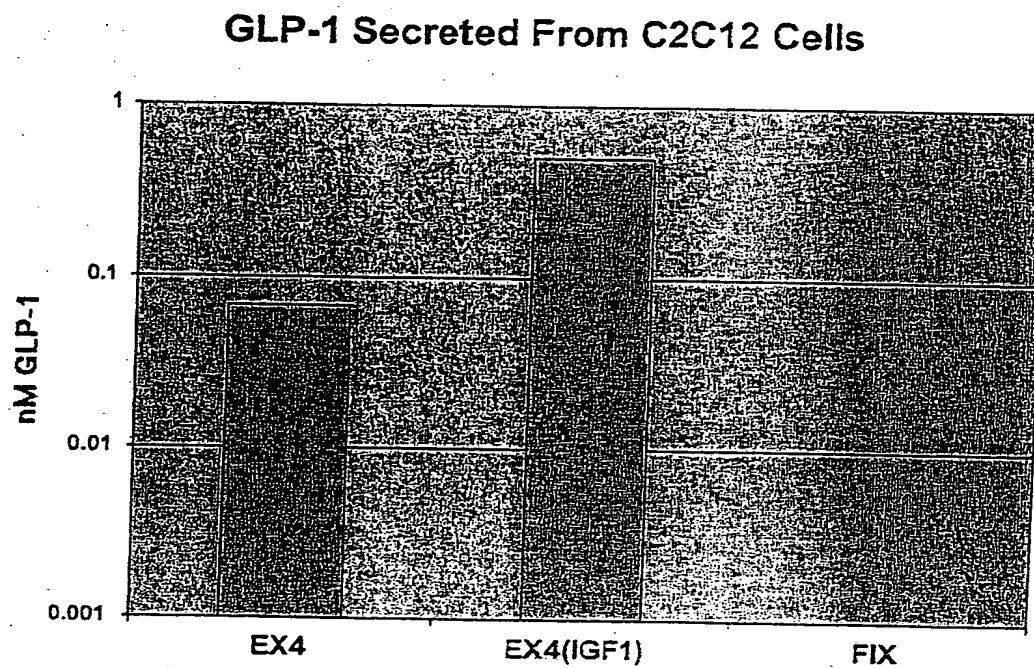


Figure 14

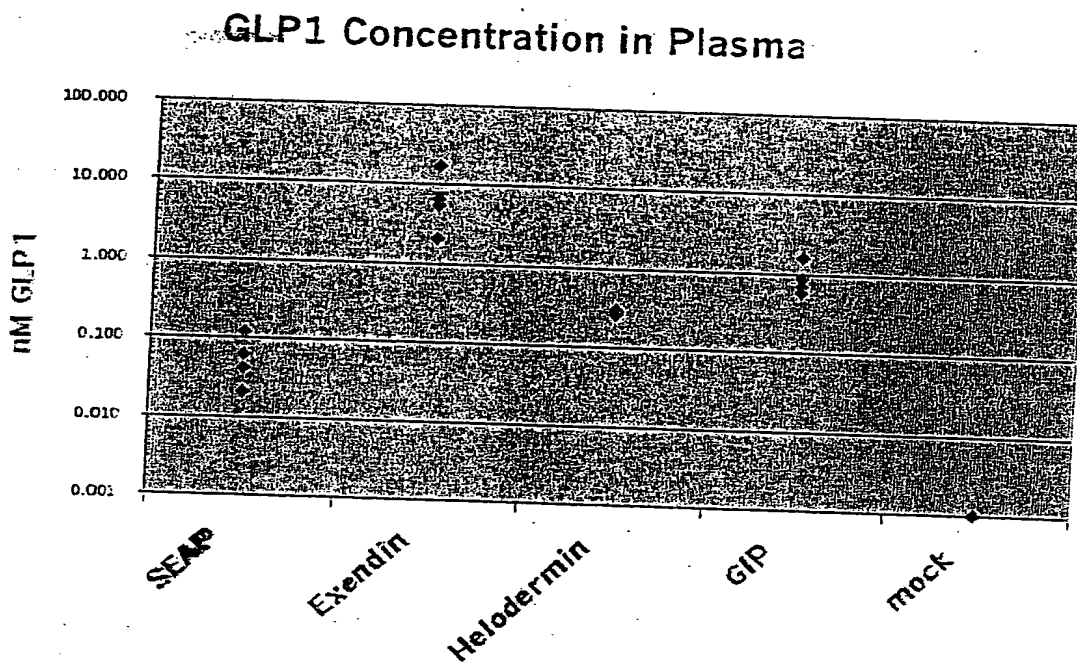


Figure 15

Blood Glucose Levels in db/db and Lean Mice Treated with a
 GLP-1 Expression Vector

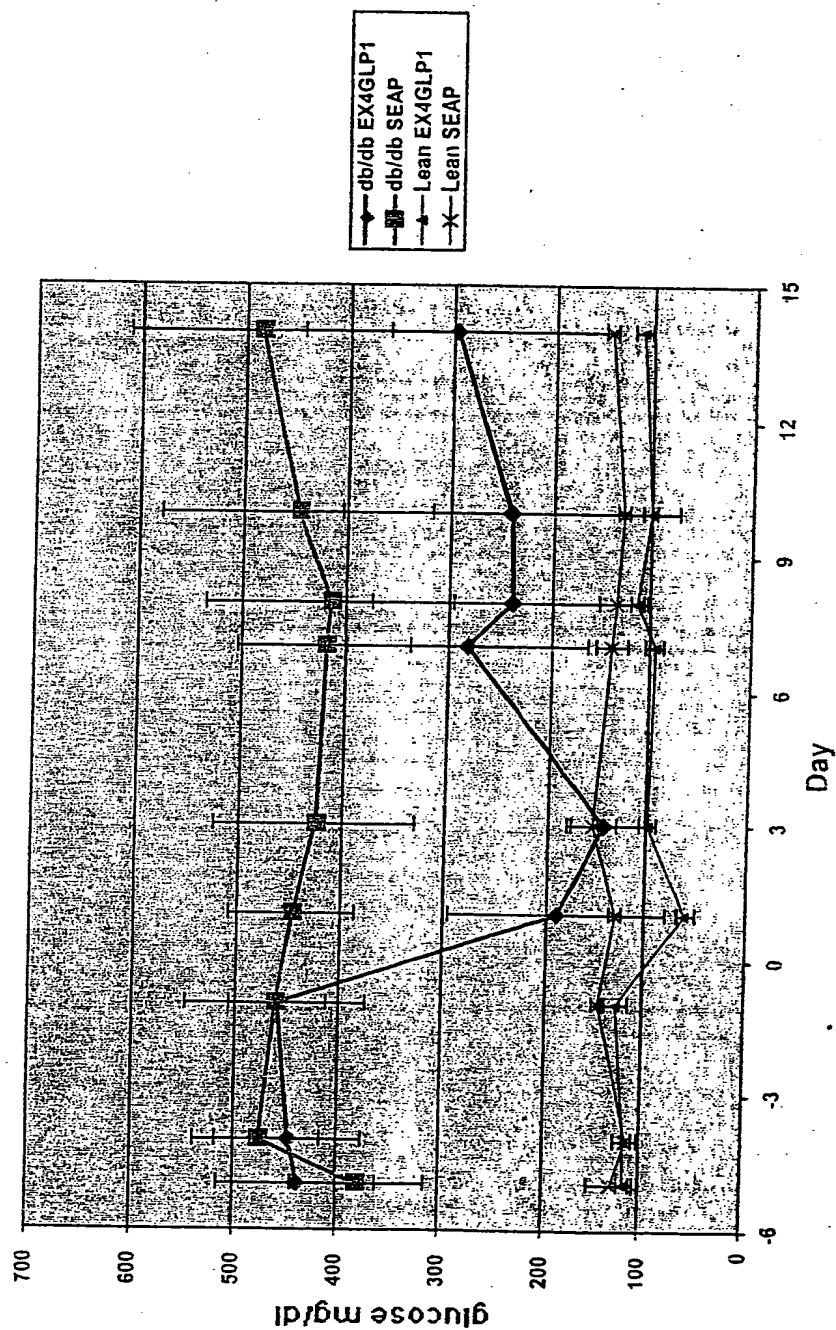


Figure 16

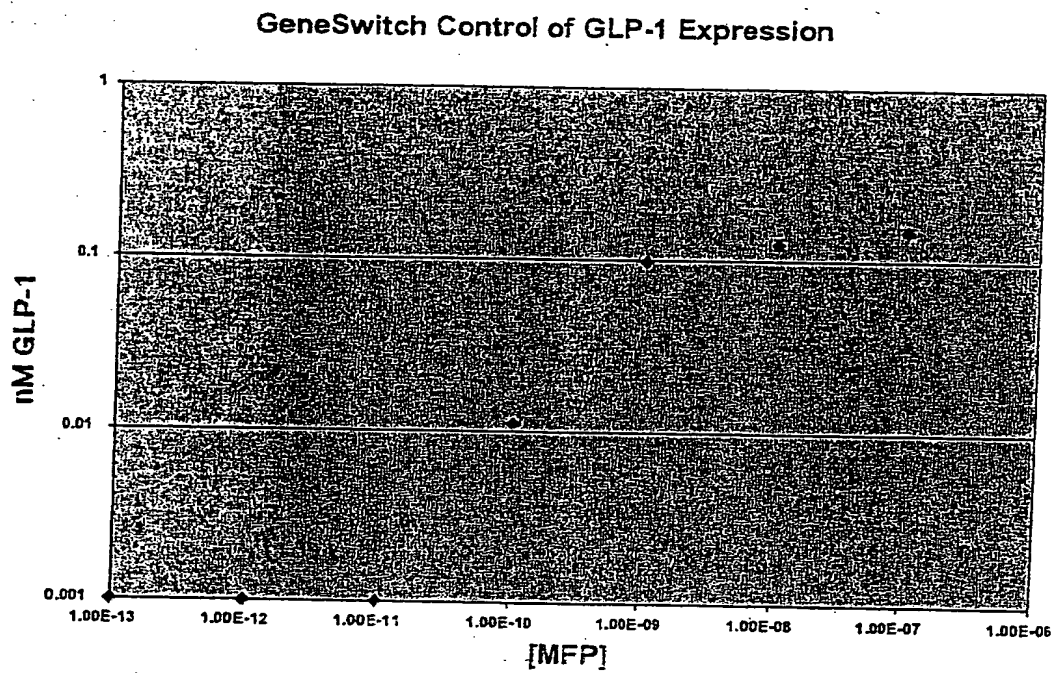


Figure 17

Examples of Modified GLP-1

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys (SEQ ID NO:23)

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵ (SEQ ID NO: 24)

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg (SEQ ID NO:25)

His⁷-Val-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:26)

His⁷-Ala-Gln-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:27)

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Thr-Ser-Lys-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷ (SEQ ID NO:28)

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Lys-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:29)

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-D-GLN³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:30)

Figure 18A

Asp-Glu-Phe-Glu-Arg-His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-
Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-
COOH (SEQ ID NO:31)

Glu-Phe-Glu-Arg-His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-
Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-
COOH (SEQ ID NO:32)

Arg-His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-
Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID
NO:33)

Figure 18B

Figure 19

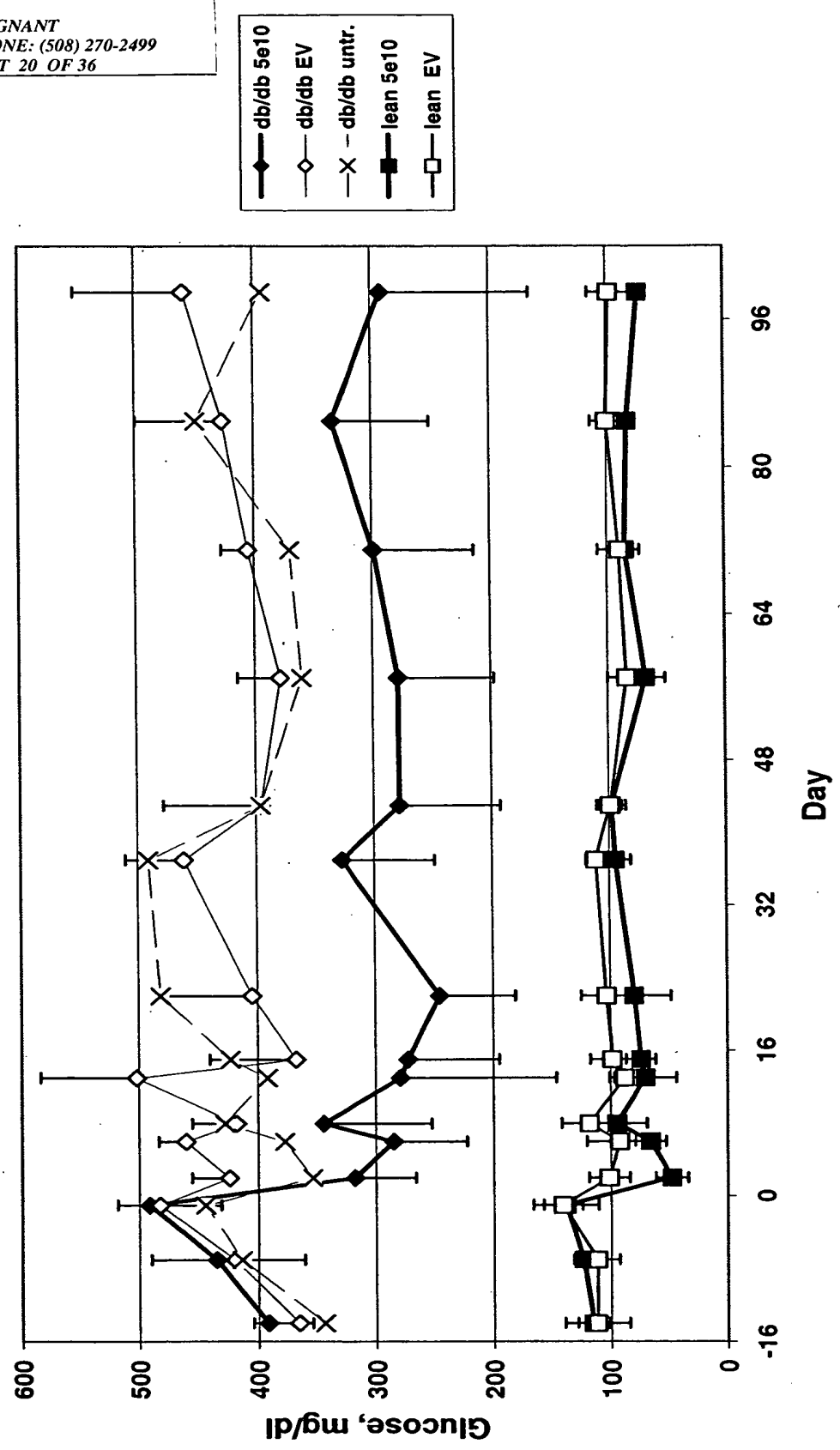


Figure 20

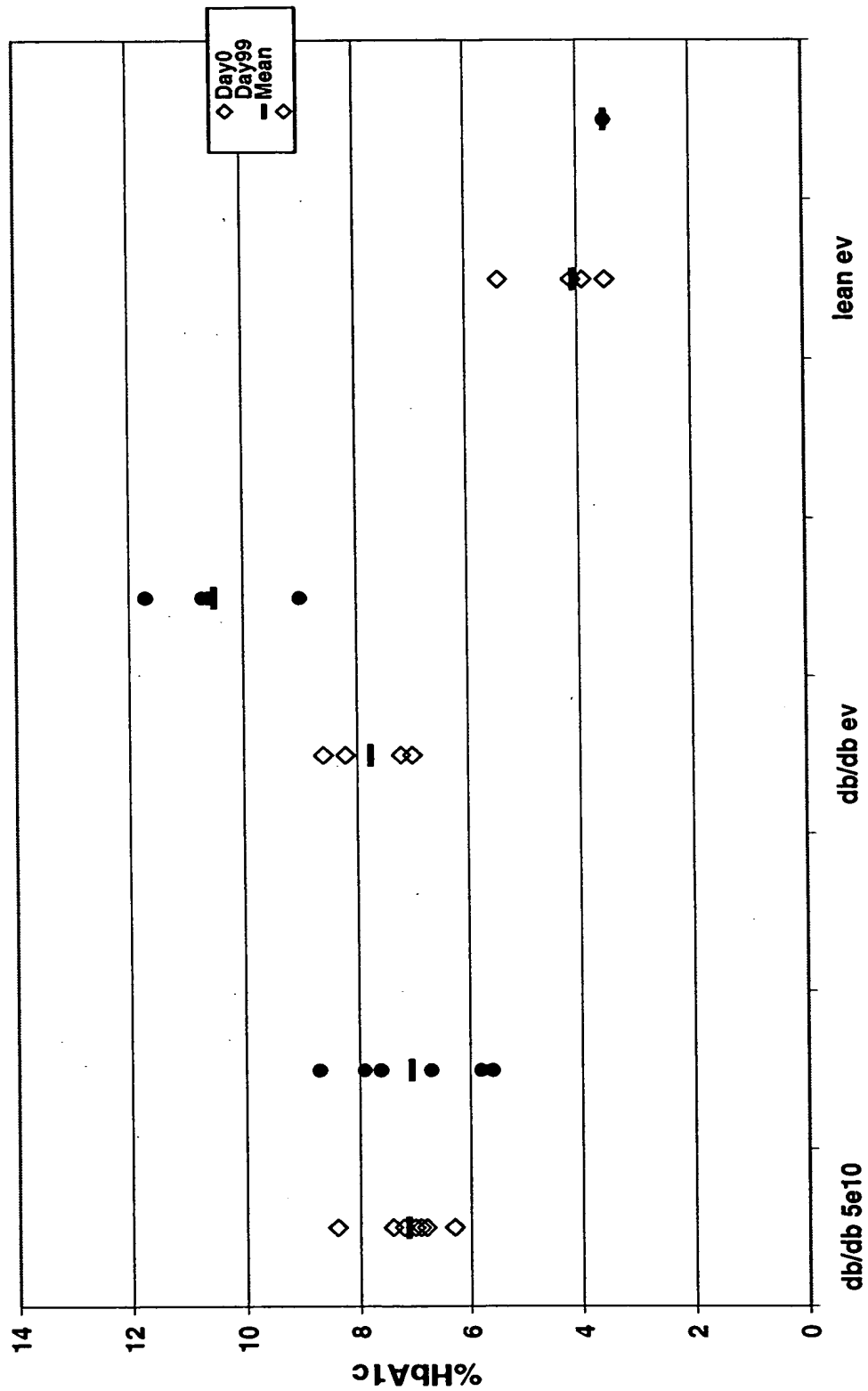


Figure 21

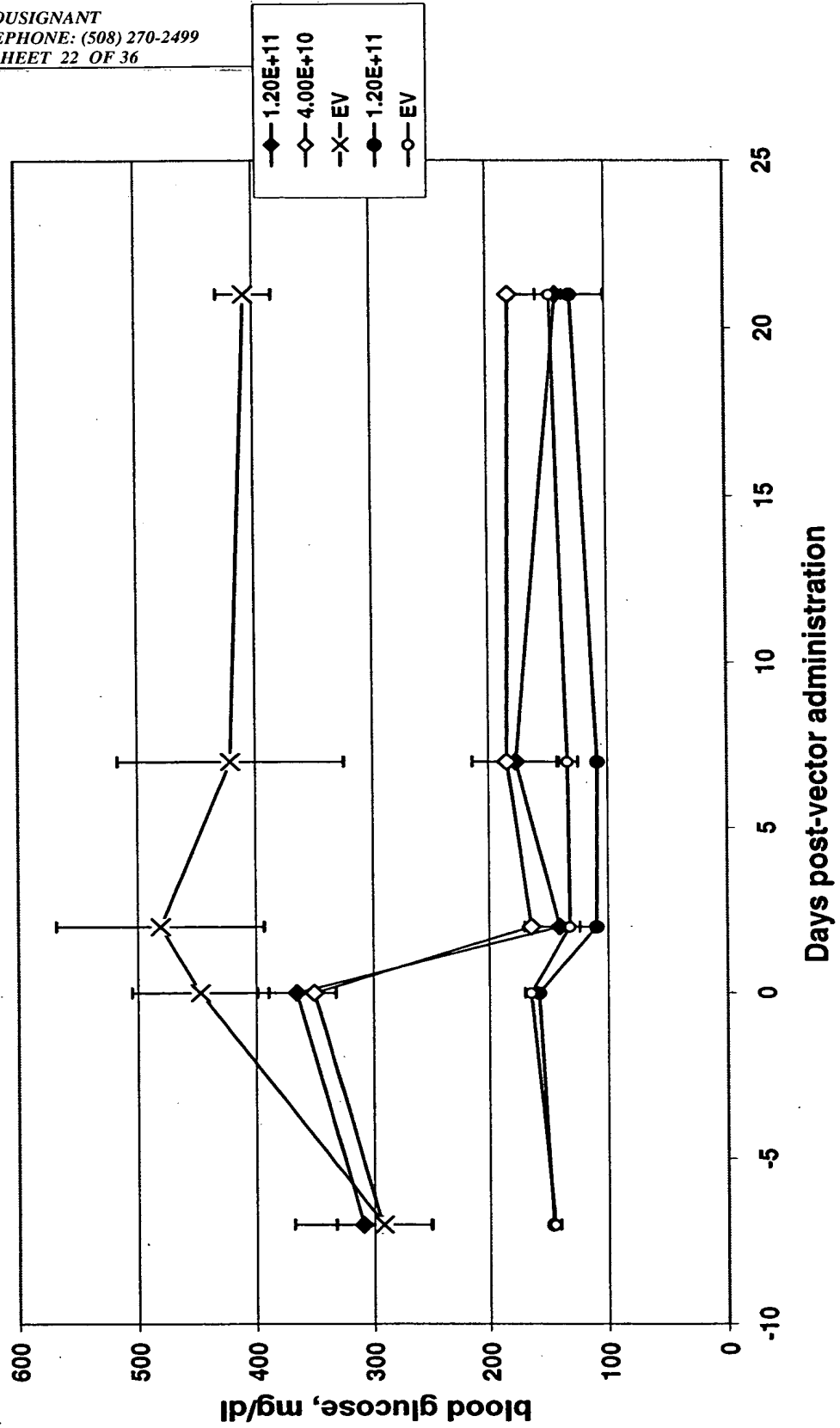


Figure 22

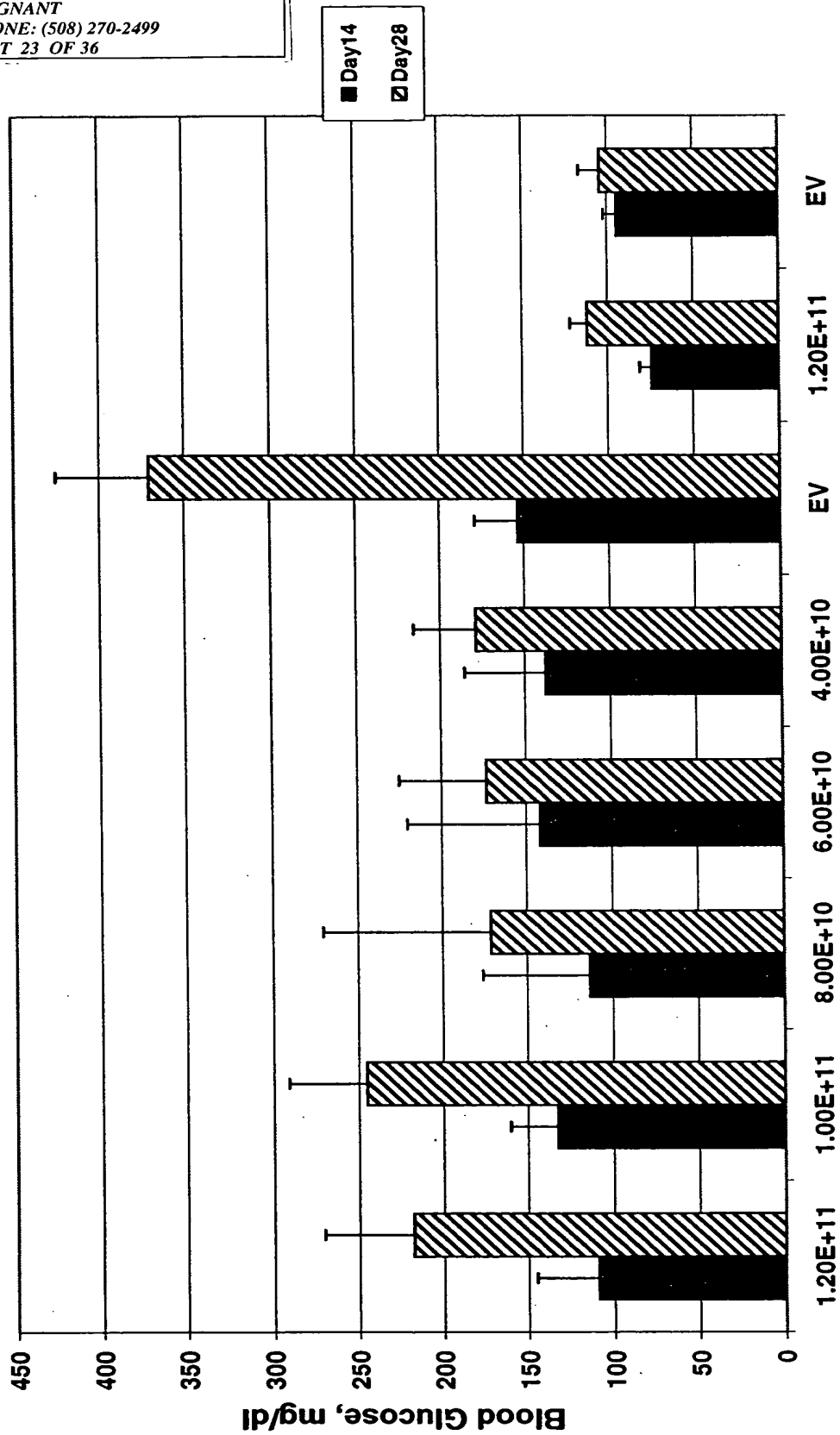
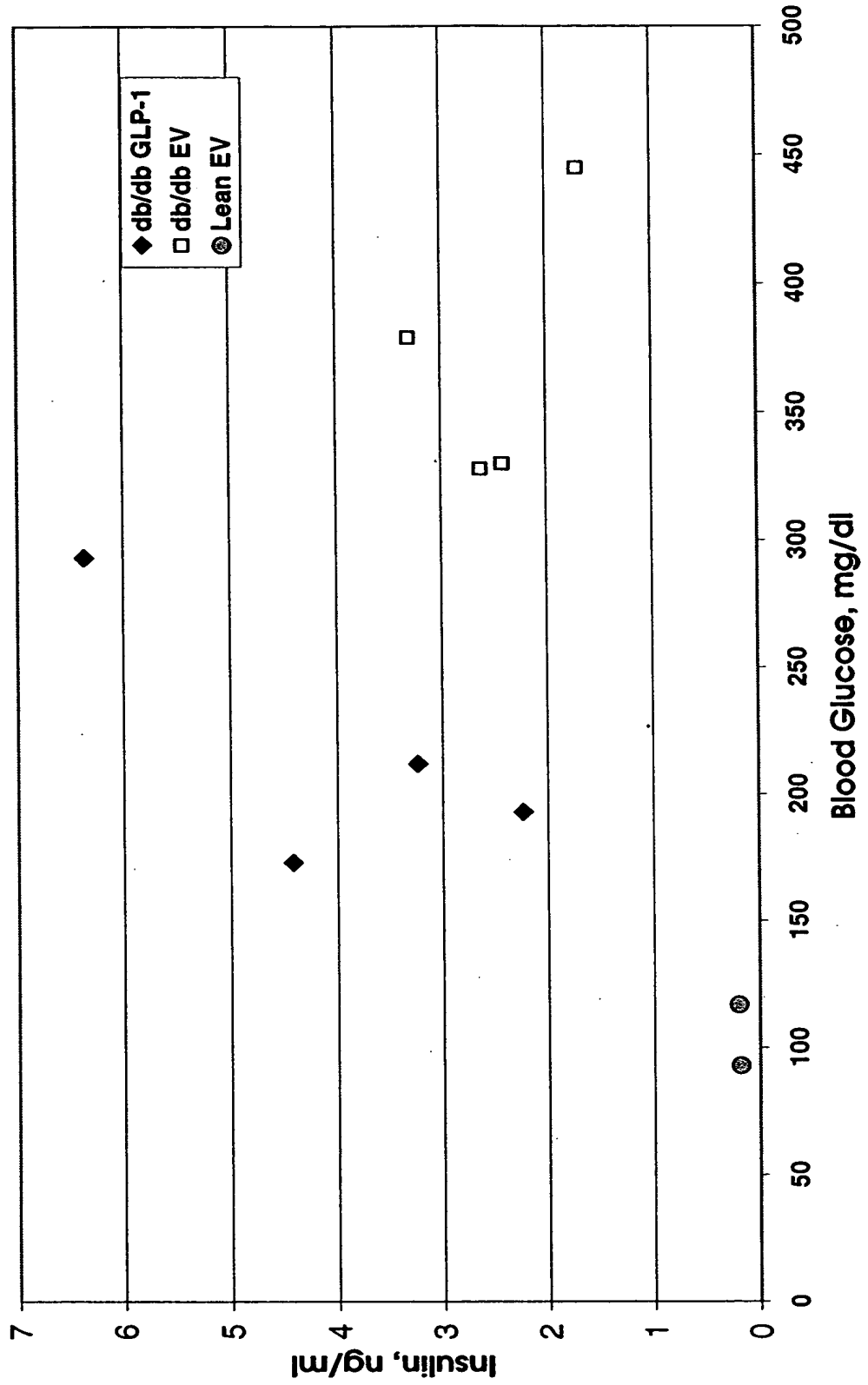


Figure 23



Day 2
Day 21

Figure 24

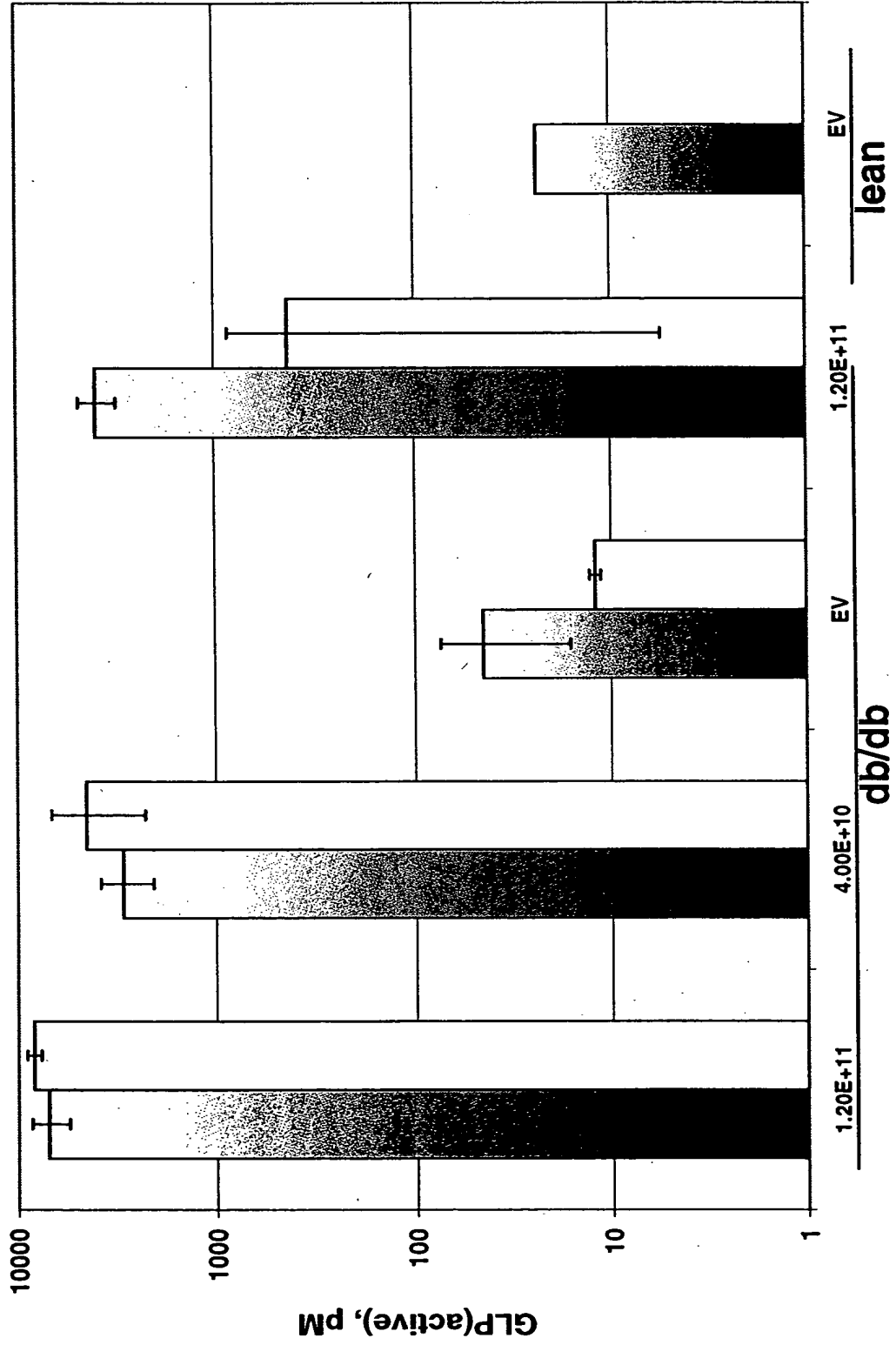


Figure 25

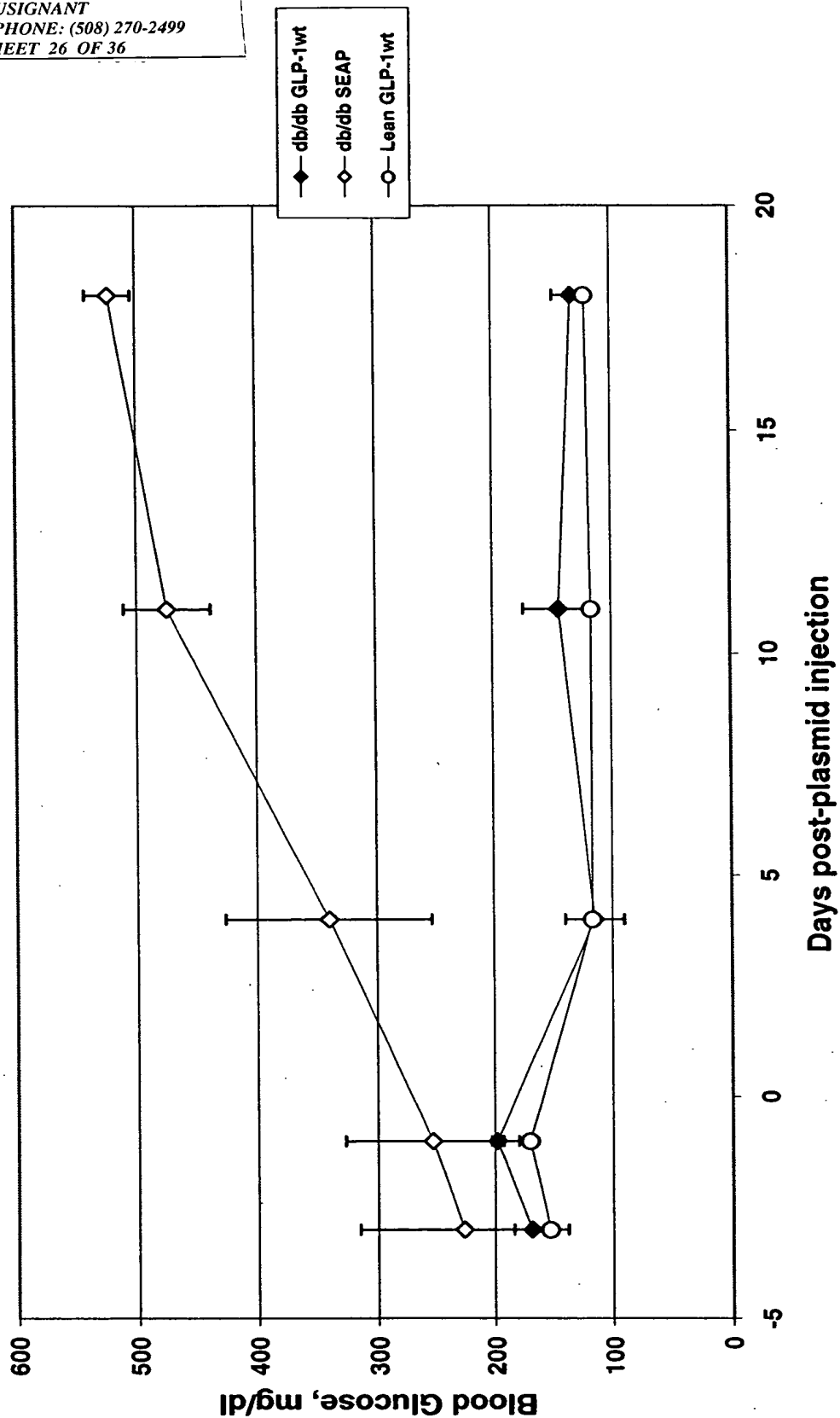


Figure 26

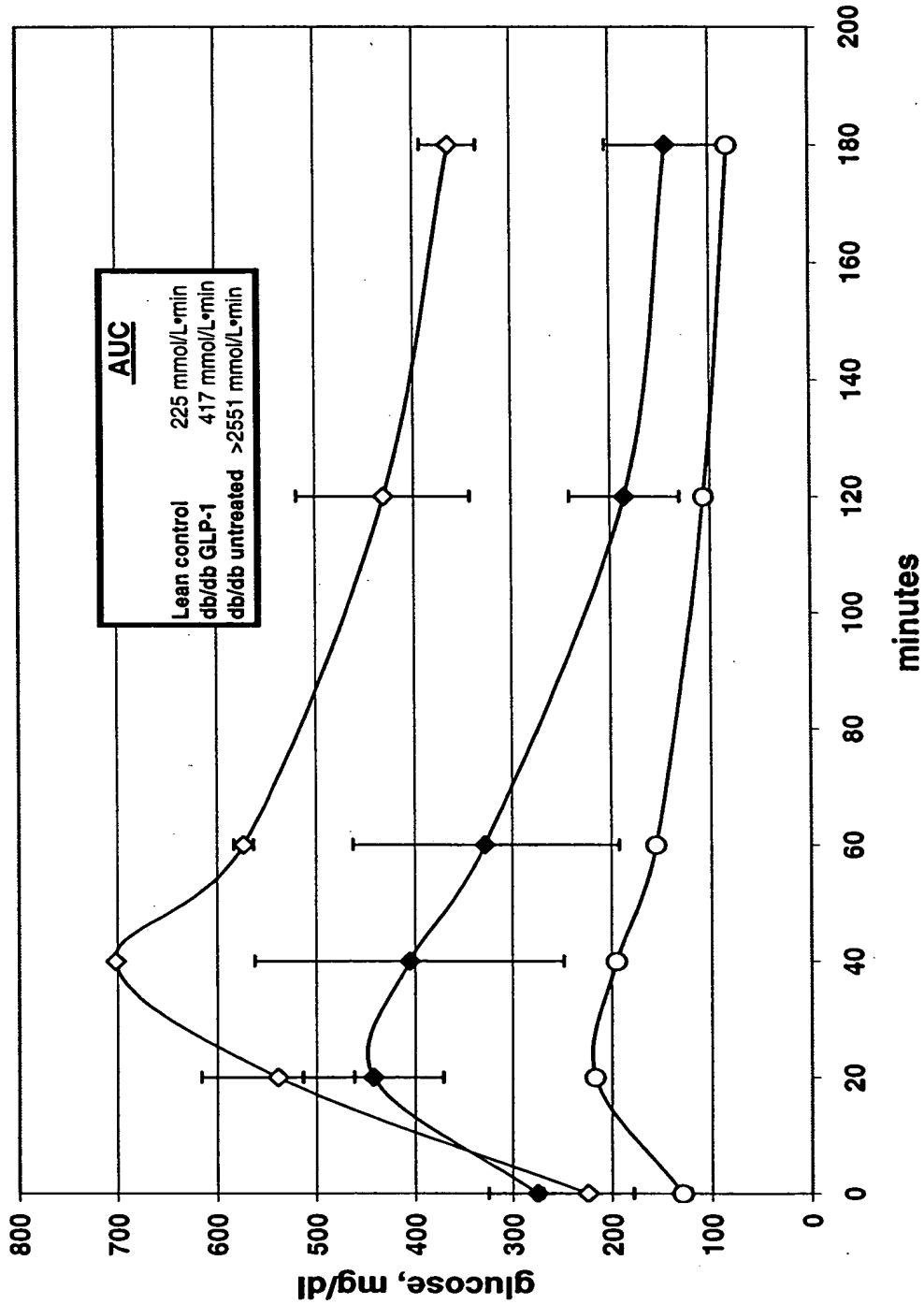


Figure 27

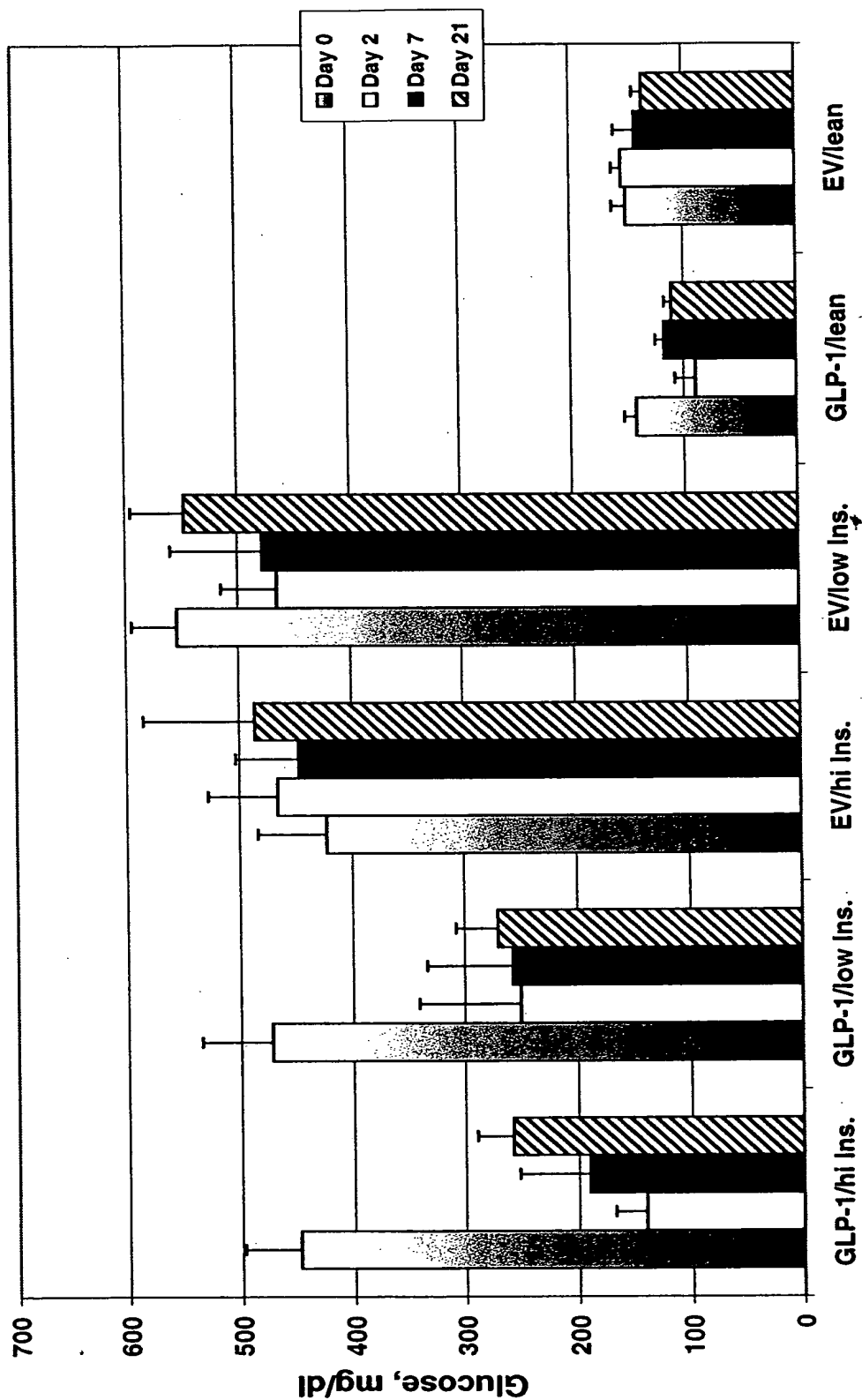


Figure 28

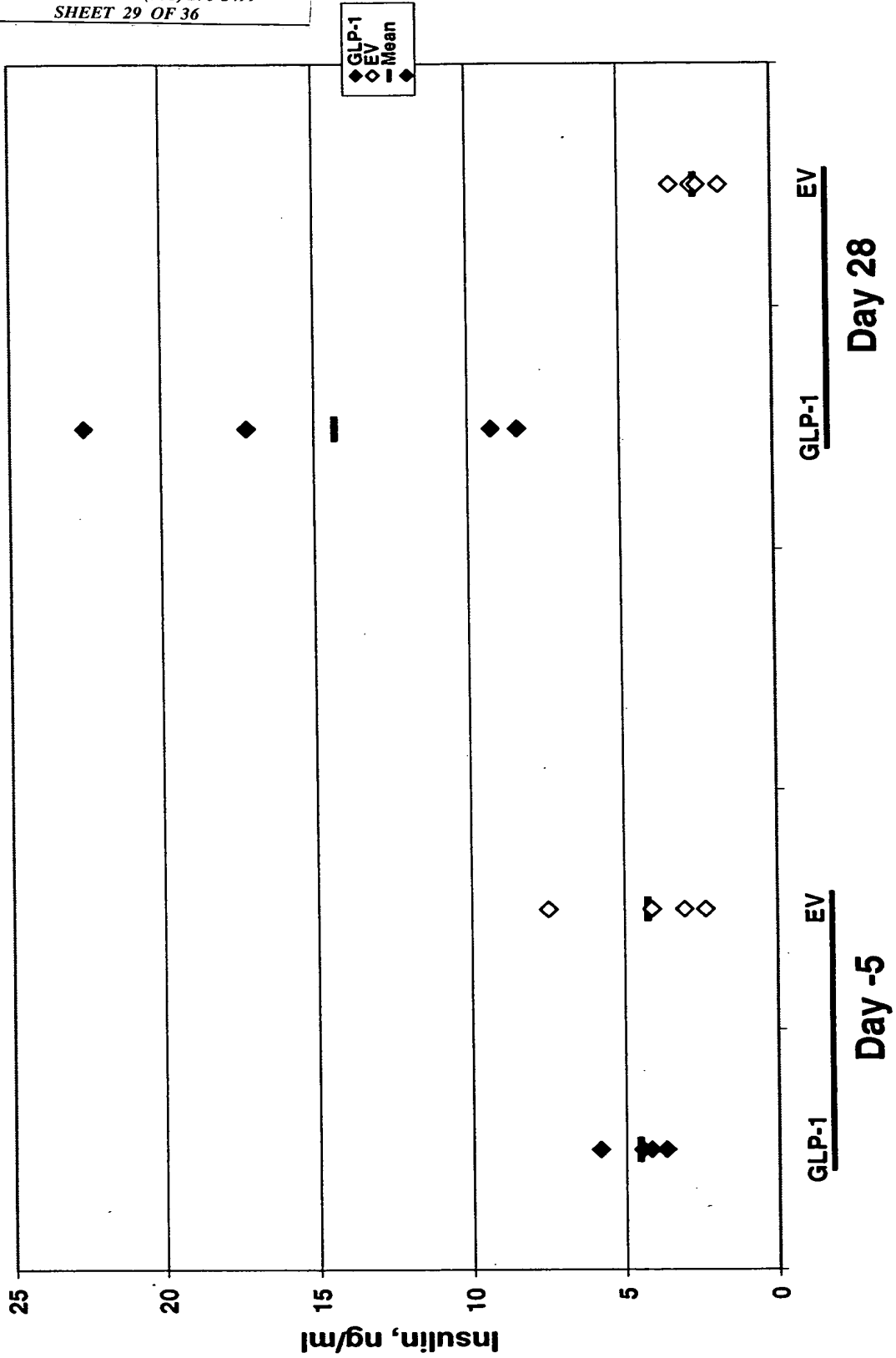


Figure 29

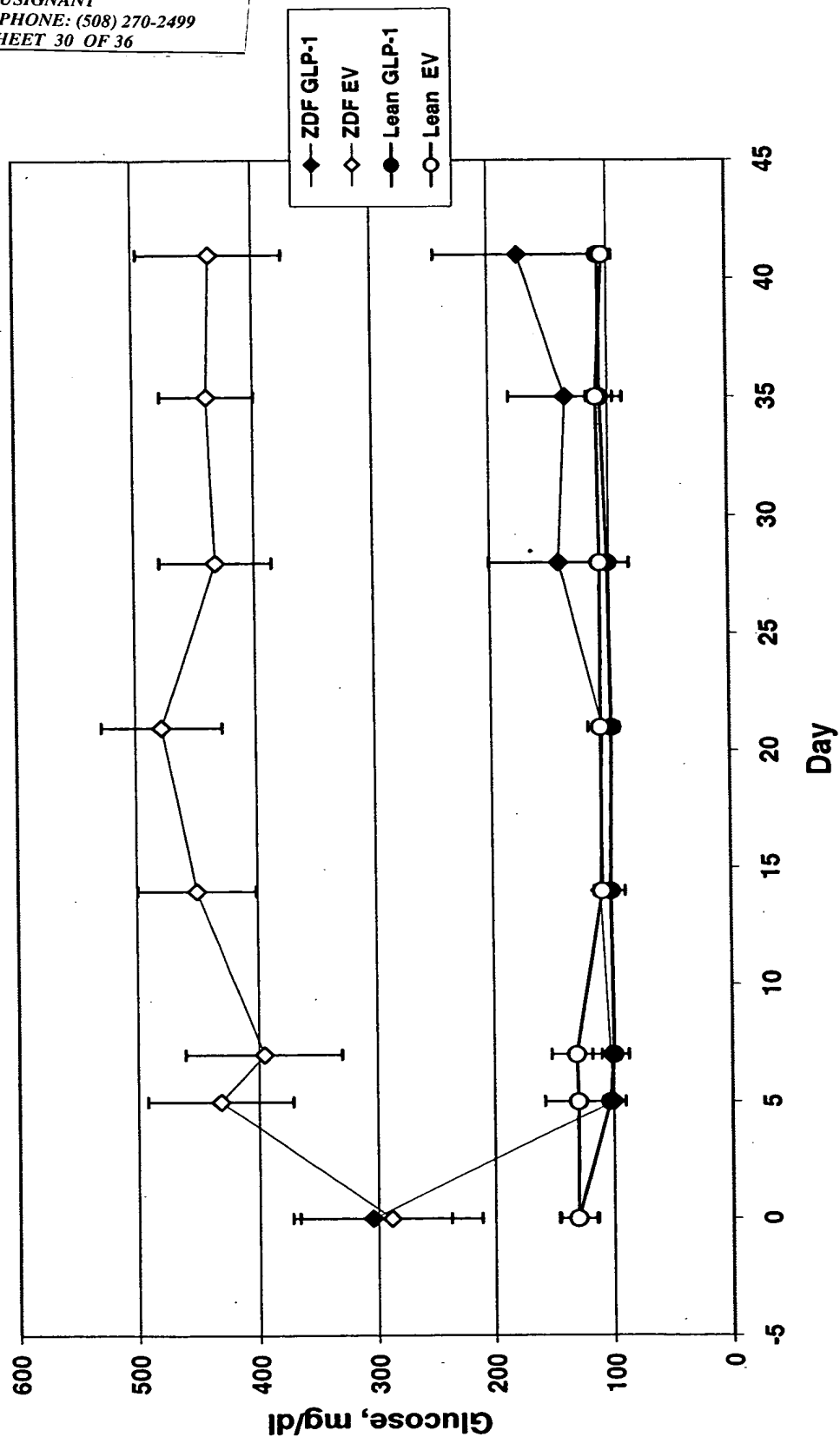


Figure 30

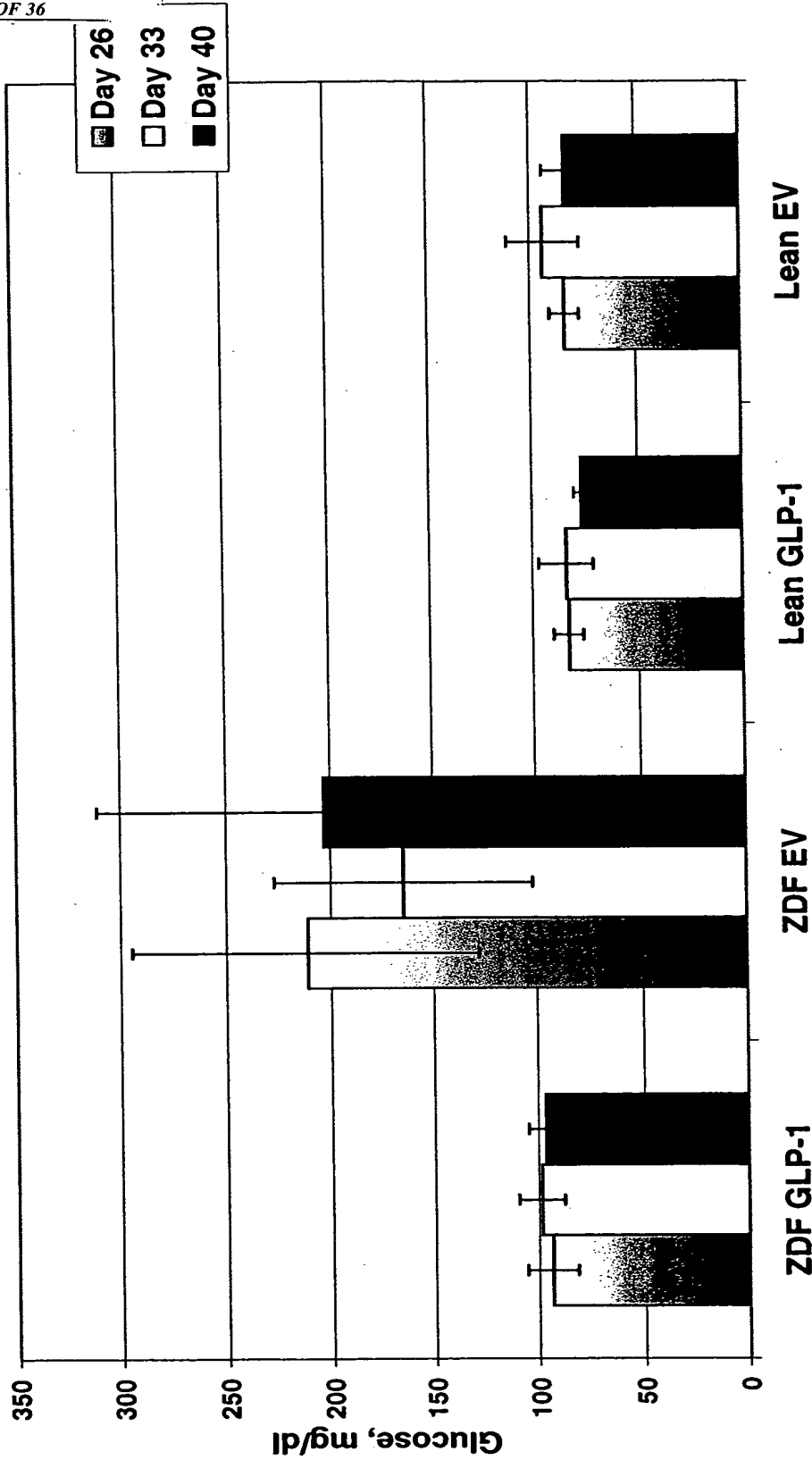
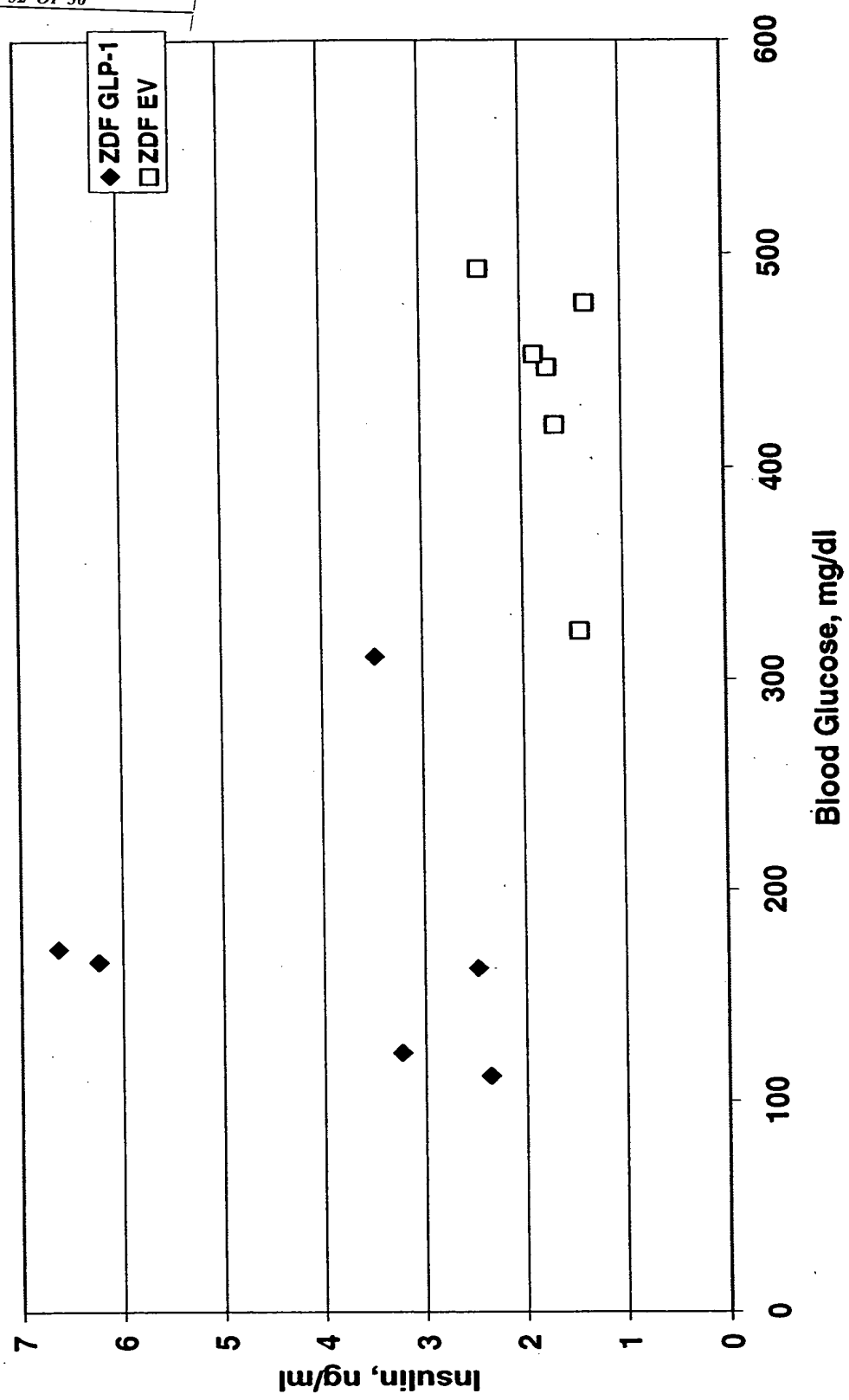


Figure 31



Day 5
 Day 28
 Day 41

Figure 32

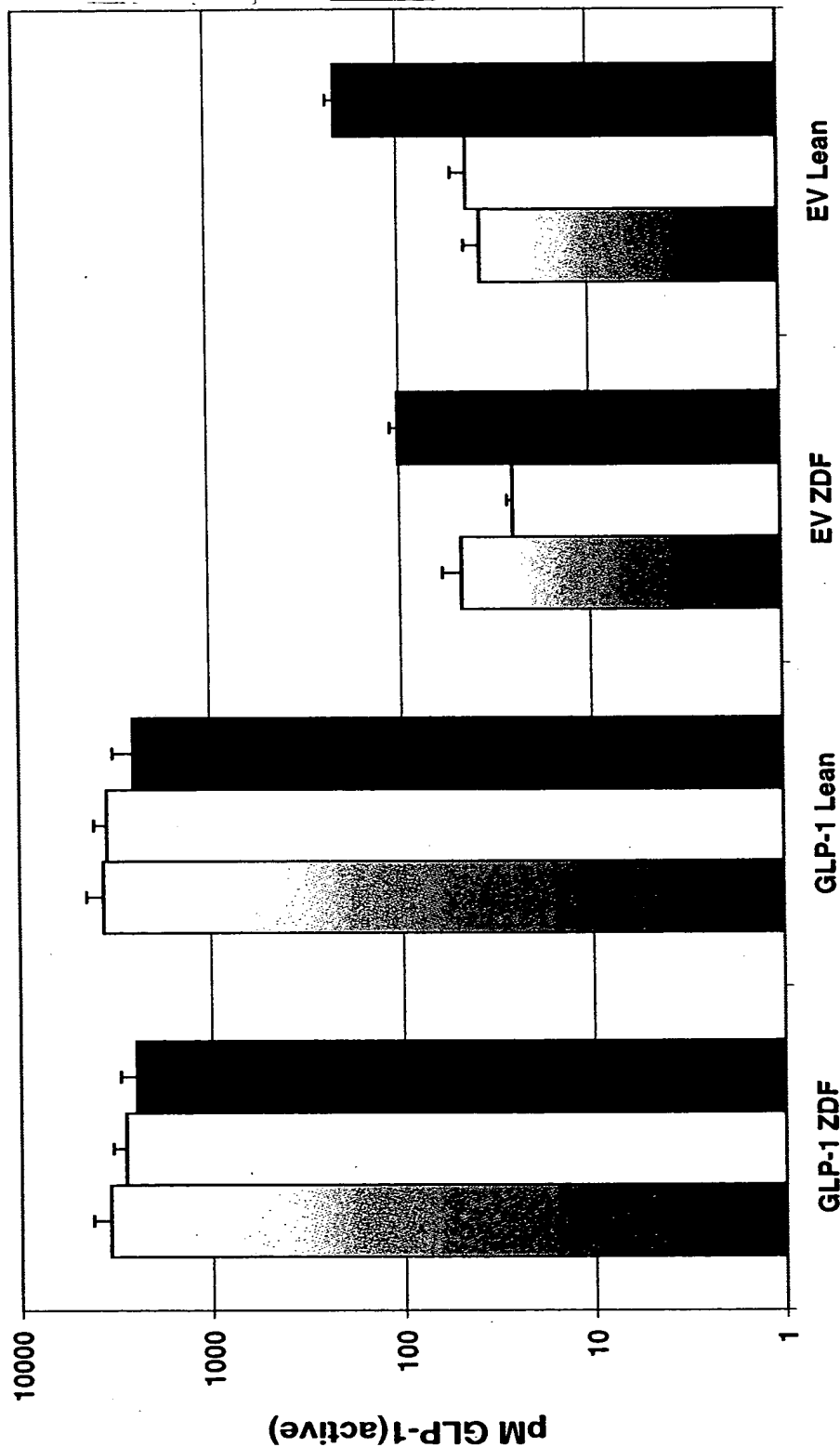


Figure 33

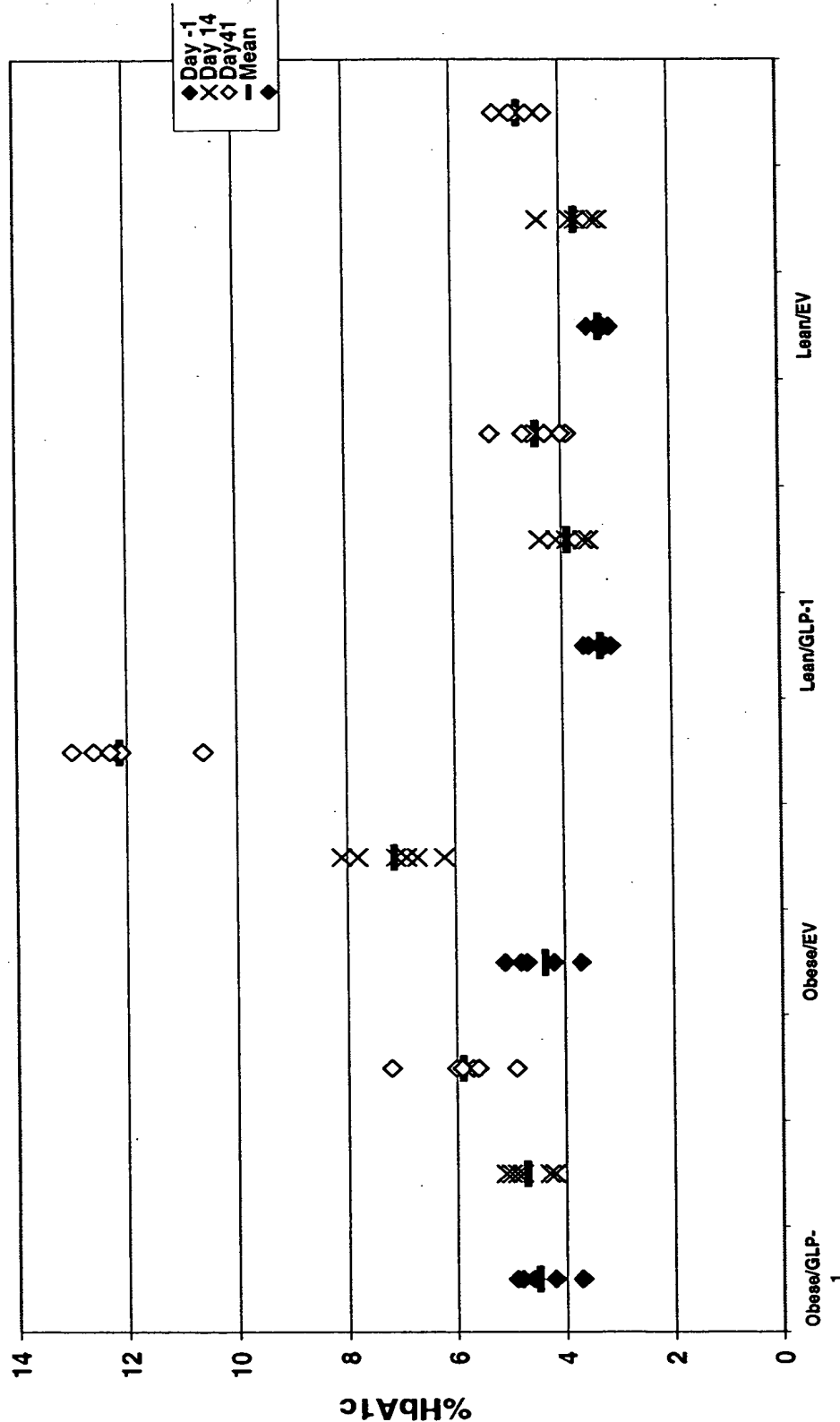


Figure 34

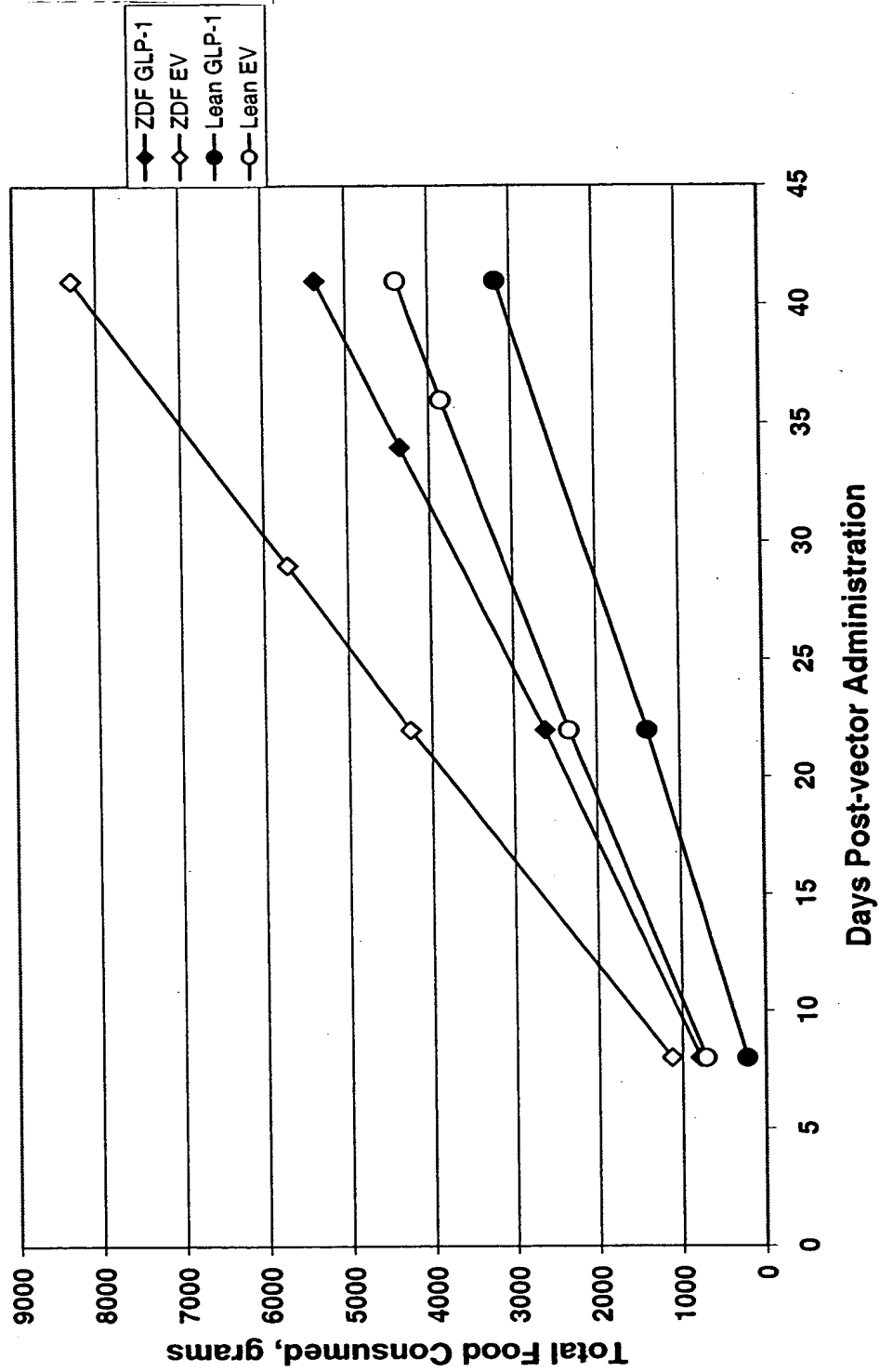


Figure 35

